FACILE DEPROTECTION OF FMOC PROTECTED AMINO GROUPS

Cross Reference To Related Applications

[0001] This application claims the benefit of U.S. Provisional Application No. 60/227,894, filed on August 25, 2000.

Field Of The Invention

[0002] The present invention relates to a novel method of deprotecting a Fmoc protected amino group.

Background Of The Invention

[0003] Peptide synthesis involves building a complex molecule by undertaking a variety of chemical transformations. These chemical transformations can require protection of functional groups to render them unavailable as reactive centers. Protected functional groups are subsequently deprotected to facilitate derivatization of the desired molecule.

[0004] One of the functional groups that is routinely protected and deprotected during peptide synthesis is an amino group. Protection of the amino group involves establishing a covalent bond between the nitrogen atom of the amino group and a protecting group, while the deprotection step involves breaking this covalent bond to restore the amino group to its reactive free base form.

[0005] Different protecting groups have been used to protect an amino group to render it unreactive, and include the Boc, benzyloxycarbonyl ("CBZ"), allyloxycarbonyl ("Alloc"), β-(trimethylsilyl)-ethoxycarbonyl ("Teoc") and Fmoc protecting groups. Procedures for protecting and deprotecting amino groups using these protecting groups are described in Protective Groups in Organic Synthesis, 3rd edition, T. W. Greene and P. G. M. Wuts, 1991. Molecules bound to solid supports or polymeric material and comprising amino groups protected with a Fmoc group are generally treated with piperidine or an equivalent base in DMF to facilitate the deprotection of the Fmoc protected amino group. This method works well and washing the deprotected solid bound molecule with an suitable solvent renders a clean product.

[0006] However, it is not convenient to deprotecting an amino group in solution phase using the above procedure. The difficulty arises from the fact that piperidine and similar bases along with solvents like DMF are high boiling and are difficult to remove from the unprotected amino product. Bases, such as piperidine, also tend to form a covalent adduct with dibenzofulvene which can also contaminate the final product. Thus, there is a need for a

procedure to deprotect Fmoc protected amino groups to provide a clean product in solid as well as solution phase reactions.

Summary Of The Invention

[0007] The invention relates to a method for deprotecting a Fmoc protected amino group.

[0008] One embodiment of the invention pertains to a method for deprotecting a Fmoc protected amino group comprising treating in an suitable medium the protected amino group with a base in the presence of a thiol compound to yield a deprotected amino group.

[0009] Another embodiment of the invention relates to a method for deprotecting a Fmoc protected amino group having the formula Fmoc-NR^1R^2, comprising treating in a suitable medium the protected amino group with a base in the presence of a thiol compound to yield a deprotected amino group having the Formula HNR^1R^2; wherein R^1 and R^2 are moieties that bind to an amino group to form a stable compound.

[00010] Yet another embodiment of the invention pertains to a method for deprotecting a Fmoc protected amino group comprising treating in a suitable medium the protected amino group with a base in the presence of a thiol compound having the formula R^3-SH to yield a deprotected amino group; wherein R^3 is selected from the group consisting of aliphatic, aryl, heteroaryl and heterocycloalkyl moieties.

Detailed Description Of The Invention

Definitions

[00011] The following terms and phrases as used herein have the following meaning, unless indicated otherwise.

[00012] The term "base" is intended to mean an organic or inorganic substance with a pKa of greater than about 8. Exemplary bases include, by way of illustration and not limitation, DBU, pyridine, triethylamine, lutidine, diisopropylethylamine, piperidine, 1,5-diazabicyclo[4.3.0]non-5-ene and mixtures thereof.

[00013] "Suitable medium" as used herein, is meant to indicate a medium/solvent which is compatible with the reaction conditions and able to facilitate in the deprotection of the amino group. Representative examples of an suitable medium are THF, dioxane, toluene, DMF, dimethylsulfoxide, dimethyl acetamide, DCM, N-methyl pyrrolidinone, methanol, isopropanol, acetonitrile, hexanes, pyridine, benzene, a pure thiol and mixtures thereof. A list of suitable

solvents can be found in *Tetrahedron Letters* 39:8451-54 (1998), which is incorporated herein by reference.

[00014] The term "thiol compound" is a compound comprising a thiol moiety attached to a aliphatic, aryl, heteroaryl or a heterocycloalkyl moiety. The thiol compound can also be written as R^3-SH, wherein R^3 is selected from the group consisting of aliphatic, aryl, heteroaryl and heterocycloalkyl moieties. Exemplary thiol compounds include by way of illustration, octane thiol, benzyl mercaptan, hexane thiol, cyclohexylmethane thiol, cyclohexane thiol, thiophenol, and thiol resins such as N-(2-mercaptp ethyl)aminomethyl polystyrene resin.

[00015] The term "aliphatic" includes "alkyl" and "cycloalkyl" moieties and is meant to indicate a saturated or partially unsaturated hydrocarbon moiety containing 1 to 14 carbon atoms. The aliphatic moiety is generally attached to at least one other atom, and can be a straight chain, branched or cyclic. An example of a partially unsaturated aliphatic moiety is an "alkelene" group which has at least one center of unsaturation, i.e., a double bond. Illustrative examples are butene, butadiene, propene, and pentene. A "cycloalkyl" moiety is a saturated or partially unsaturated 3 to 10 carbon monocyclic or bicyclic hydrocarbon moiety. The term straight chain alkyl moiety is meant to represent an unbranched hydrocarbon moiety of up to 8 carbon atoms such as n-pentyl. The aliphatic moiety can be substituted with 1-3 substituents selected from the group consisting of alkoxy, =O, -N(C_{1-4}alkyl)$_2$, -OH, -C(O)-O-C_{1-8}alkyl, -S-C_{1-4}alkyl, cyano (-C≡N), -CF_3, halo, aryl, heteroaryl and -C_{1-4}alkylester.

[00016] The term "aryl" means an aromatic monocyclic, bicyclic, or a fused polycyclic hydrocarbon moiety containing the number of carbon atoms indicated, and which can be optionally substituted with 1-3 substituents selected from the group consisting of alkoxy, =O, -N(C_{1-4}alkyl)$_2$, -OH, -C(O)-O-C_{1-8}alkyl, -S-C_{1-4}alkyl, cyano (-C≡N), -CF_3, halo, aryl, heteroaryl and -C_{1-4}alkylester. Thus a C_6-C_{14} aryl group includes phenyl, naphthyl, anthracenyl, etc. The term "heteroaryl" means aryl, as defined above, wherein one or more of the carbon atoms is replaced by a heteroatom chosen from N, O, and S. The heteroatoms can exist in any of their chemically allowed oxidation states, e.g., sulfur can exist as a sulfide, sulfoxide, or sulfone. Each heteroaryl ring comprises from 5 to 14 atoms and examples include thienyl, furyl, pyrrolyl, indolyl, pyrimidinyl, isoxazolyl, purinyl, imidazolyl, pyridyl, pyrazolyl, quinolyl, and pyrazinyl.

[00017] The term "heterocycloalkyl" moiety means a cycloalkyl, as defined above, where one or more of the carbon atoms of the cycloalkyl moiety are replaced by a heteroatom selected

from the group consisting of N, NR, O, S(O), $S(O)_2$ and S, wherein R is $-C_{1-6}$alkyl or hydrogen. Illustrative heterocycloalkyl moieties include morpholinyl, indolinyl, piperidyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, quinuclidinyl and morpholinyl. The heterocycloalkyl moiety can be optionally substituted with 1-3 substituents selected from the group consisting of alkoxy, =O, $-N(C_{1-4}alkyl)_2$, -OH, $-C(O)-O-C_{1-8}$alkyl, $-S-C_{1-4}$alkyl, cyano (-C≡N), $-CF_3$, halo, aryl, heteroaryl and $-C_{1-4}$alkylester.

[00018] The term "alkoxy" represents an oxygen atom attached to an alkyl moiety and comprises from 1-6 carbon atoms.

[00019] A "deprotected amino group" as used herein means a primary amine, a secondary amine or aniline.

[00020] The present invention provides a method for deprotecting a Fmoc protected amino group comprising treating in a suitable medium the protected amino group with a base in the presence of a thiol compound to yield a deprotected amino group.

[00021] The thiol compound can be bound to a solid support or it can be in solution. A preferred embodiment provides a method wherein the thiol compound is aliphatic. In another preferred embodiment the thiol group is attached to the rest of the thiol compound by a methylene group.

[00022] As noted above, examples of suitable media that can be used in the method of the invention include, by way of example and not limitation, THF, dioxane, toluene, DMF, dimethylsulfoxide, dimethyl acetamide, DCM, N-methyl pyrrolidinone, methanol, isopropanol, acetonitrile, hexanes, pyridine, benzene, a pure thiol and mixtures thereof. Preferred media include, THF, methanol, isopropanol, dioxane, toluene, acetonitrile, hexanes, pyridine, benzene and mixtures thereof. In one embodiment of the invention, the medium used in the method is an organic solvent with a boiling point below about 120°C.

Abbreviations

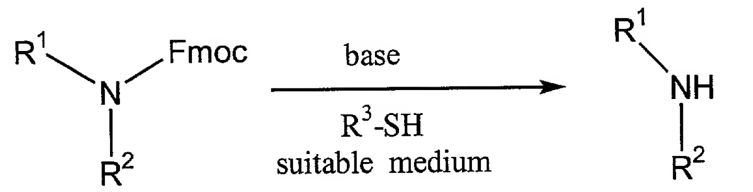
AMC	7-amino-4-methylcoumarin
Arg	arginine
Asp	aspartic acid
Asn	asparagine
Boc	*t*-butoxy carbonyl
Cit	citraline

Cys	cysteine
DBU	1,8-diazabicyclo[5.4.o]undec-7-ene
DCM	dichloromethane
DMF	dimethylformamide
EtOH	ethanol
Et_2O	diethyl ether
Fmoc	9-fluoromethoxy carbonyl
Gln	glycine
Glu	glutamic acid
Lys	lysine
O-*t*-BU	tert-butyl ether
Orn:	ornithine
Pbf	2,2,4,6,7-pentamethyl di-hydrobenzofuran-5-sulfonyl
Ser	serine
t-Bu	tert-butyl
THF	tetrahydrofuran
Thr	threonine
Trp	tryptophan
Trt	trityl
Tyr	tyrosine

Experimental

[00023] The method of the present invention is further illustrated by the reaction Scheme I and synthetic procedures discussed below.

Scheme I



Formula I

Formula II

[00024] R^1 and R^2 are moieties that bind to an amino group to form a stable compound and R^3-SH represents a compound comprising a thiol group. The R^3 substituent can be selected from the group consisting of aliphatic, aryl, heteroaryl and heterocycloalkyl moieties.

[00025] "Moieties that bind to an amino group to form a stable compound" are also commonly referred to as "suitable amine substituent(s)" and represent substituents which are capable of forming a covalent bond with an amine group to form a compound of Formula I and/or II. Illustrative examples of suitable amine substituents are optionally substituted alkyls, optionally substituted aryls, optionally substituted heteroaryls and optionally substituted alkoxy groups. Such groups include, by way of illustration and not limitation, 2-hydroxy-1-hydroxymethyl-2-phenyl-ethylamino, 2-hydroxy-1-hydroxymethyl-3-methyl-pentylamino, 1-benzyl-2-hydroxy-ethylamino, 1-hydroxymethyl-3-methyl-butylamino, 4-amino-piperidine-1-carboxylic acid ethyl ester, 2-acetylamino-ethylamino, 2-diethylamino-ethylamino, 2-(2-hydroxy-ethoxy)-ethylamino, 3-diethylamino-propylamino, 3-hydroxy-propylamino, 6-hydroxy-hexylamino, 3-imidazol-1-yl-propylamino, 2-(4-sulfamoyl-phenyl)-ethylamino, 3-(4-methyl-piperazin-1-yl)-propylamino, 2-dimethylamino-1-methyl-ethylamino, 2-[bis-(2-hydroxy-ethyl)-amino]-ethylamino, 1-carbamoyl-2-phenyl-ethylamino, 2-dibutylamino-ethylamino, 5-hydroxy-4,4-dimethyl-pentylamino, 3-dimethylamino-2,2-dimethyl-propylamino, 2-(butyl-ethyl-amino)-ethylamino, 2-diisobutylamino-ethylamino, 2-hydroxy-butylamino, 3-hydroxy-2,2-dimethyl-propylamino, cyclohexylamino, (5-hydroxy-1,3,3-trimethyl-cyclohexylmethyl)-amino, 1,2,3,4-tetrahydro-naphthalen-1-ylamino, cyclooctylamino, 3-(2-oxo-pyrrolidin-1-yl)-propylamino, indan-1-ylamino, (tetrahydro-furan-2-ylmethyl)-amino, 2-(1h-indol-3-yl)-ethylamino, (benzo[1,3]dioxol-5-ylmethyl)-amino, 3-morpholin-4-yl-propylamino, 2-pyridin-2-yl-ethylamino, 2-hydroxy-1-methyl-2-phenyl-ethylamino, 1-methoxy-ethylamino, 1-methyl-3-phenyl-propylamino, 3-diethylamino-1-methyl-propylamino, benzylamino, 2-fluoro-

benzylamino, 2-methoxy-benzylamino, 3-trifluoromethyl-benzylamino, 2-phenylamino-ethylamino, 2-methoxy-ethylamino, phenethylamino, 2-(2-methoxy-phenyl)-ethylamino, 2-(3,4-dimethoxy-phenyl)-ethylamino, 2-(4-chloro-phenyl)-ethylamino, 2-(4-methoxy-phenyl)-ethylamino, 2-(4-hydroxy-phenyl)-ethylamino, 3,3-diphenyl-propylamino, 2,5-dimethyl-benzylamino, 2-trifluoromethyl-benzylamino, butylamino, 1,2-diethyl-pyrazolidin-4-ylamino, 3-methoxy-propylamino, 2-diisopropylamino-ethylamino, 1-isopropyl-2-methyl-propylamino, 3-m-tolylamino-pentylamino, 3-butoxy-propylamino, 1-(4-fluoro-phenyl)-ethylamino, 1-methoxymethyl-propylamino, 2,3-dimethoxy-benzylamino, 2,4-dimethoxy-benzylamino, 2-(2-chloro-6-fluoro-benzylsulfanyl)-ethylamino, 2,6-dimethoxy-benzylamino, 3,5-dimethoxy-benzylamino, 2-phenoxy-ethylamino, 1-benzyl-pyrrolidin-3-ylamino, 2-(2,3-dimethoxy-phenyl)-ethylamino, 2-(2,5-dimethoxy-phenyl)-ethylamino, 2-(2-ethoxy-phenyl)-ethylamino, 2-(3,5-dimethoxy-phenyl)-ethylamino, 2-(4-ethoxy-phenyl)-ethylamino, 2-(4-trifluoromethoxy-phenyl)-ethylamino, 2-hydroxy-1,2-diphenyl-ethylamino, 2-hydroxy-1,2-diphenyl-ethylamino, 2-(2-hydroxymethyl-phenylsulfanyl)-benzylamino, 2-(3-fluoro-phenyl)-ethylamino, 2-(2-amino-phenyl)-benzylamino, 2-(2-fluoro-phenyl)-ethylamino, 4-amino-benzylamino, 2-(3,4-dimethoxy-phenyl)-ethylamino, 1,2-dihydroxy-2-(4-methylsulfanyl-phenyl)-ethylamino, 2-hydroxy-cyclohexylamino, and 3-(methyl-phenyl-amino)-propylamino. A comprehensive list of amines substituted with a substituted with suitable substituents can be found in the Aldrich chemicals catalog, which is incorporated herein by reference.

Synthetic Procedure

[00026] Referring to Scheme I, a compound of Formula I (about 1 eq.; comprising a Fmoc protected amino group) is treated with a base (e.g., DBU; about 0.1 to 0.5 eq.) in a suitable medium (e.g., THF) in the presence of a compound comprising a thiol group (e.g., a thiol resin or octanethiol; about 5 to 15 eq.). The resulting reaction mixture is agitated at ambient temperature for up to about 60 hours. The reaction mixture is then concentrated to yield a compound of Formula II. Purification of the compound of Formula II, if necessary, can be accomplished by techniques known to one skilled in the art. Illustrative examples of such techniques are chromatography, recrystallization, trituration and the like.

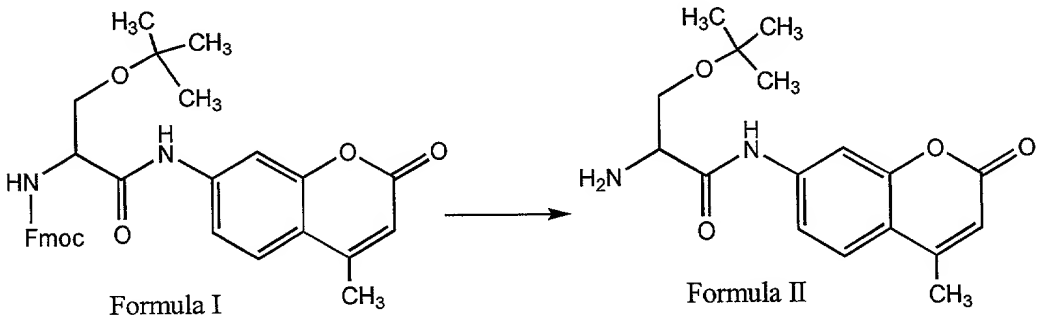
[00027] Advantages of the present invention include the quantitative removal of the amino protecting Fmoc group using a catalytic amount of DBU base (0.1 to 0.25 eq) and 5-10 eq of a thiol or thiol resin. The resin scavenges the dibenzofulvene that comes from the Fmoc group,

which can be removed by filtration, and the product can be freed from any residual amounts of DBU under reduced pressure or by trituration. This is a considerable improvement over the classical deprotection route described above where the Fmoc group is treated with piperidine or an equivalent base in DMF, to facilitate the deprotection of the Fmoc protected amino group.

Examples

[00028] The following representative examples further illustrate the method of the present invention. The compounds can be treated with a base in a suitable medium to form the corresponding unprotected amino group containing compounds of Formula II, using the method of the present invention.

Example 1



Formula I Formula II

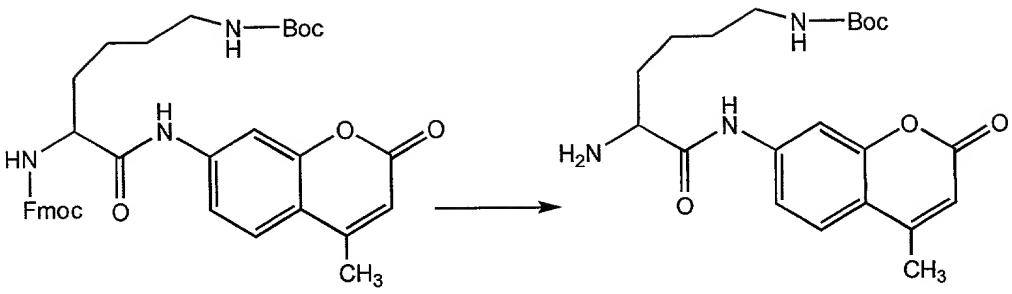
H-Lys(Boc)-AMC (Formula II)

[00029] Fmoc-Lys(Boc)-AMC (Formula I) (15.9 g, 25.5 mmol), 1-octanethiol (44.2 mL, 255 mmol), DBU (114.3 µL, 0.77 mmol, 3 mol %). Reaction time: 3.25 h. Yield 10.3 g (quant.).

MS 404 ($M+H^+$).

^1H NMR (CD_3OD) δ 7.80 (s, 1H), 7.67 (d, 1H), 7.47 (d, 1H), 6.19 (s, 1H), 3.42 (m, 1H), 2.99 (m, 2H), 2.41 (s, 3H), 1.72 (m, 2H), 1.60 (m, 2H), 1.44 (m, 2H), 1.35 (s, 9H).

Example 2



H-Orn(Boc)-AMC (Formula II)

[00030] Fmoc-Orn(Boc)-AMC (Formula I) (25.5 g, 41.7 mmol), 1-octanethiol (72 mL, 417 mmol), DBU (623 μL, 4.17 mmol, 10 mol %). Reaction time: 14 h. This compound was obtained as an oil which then was taken up in 50 mL EtOH, 1.1 eq of glacial acetic acid was added, the solution was concentrated in vacuo, taken up in DCM, and triturated with Et_2O at -20°C. Yield of acetate salt: 17.27 (92%).

MS 389 (M^+)

Example 3

H-Cit-AMC (Formula II)

[00031] Fmoc-Cit-AMC (Formula I) (16.4 g, 30 mmol), 1-octanethiol (51.2 mL, 295 mmol), DBU (441 μL, 2.94 mmol, 10 mol %). Reaction time: 14 h: Yield: 8.35 (85%).

MS 333 ($M+H^+$)

H-Ser(*t*-Bu)-AMC (Formula II)

[00032] Fmoc-Ser(*t*-Bu)-AMC (Formula I) (19.3 g, 35.7 mmol), 1-octanethiol (62.0 mL, 357 mmol), DBU (533 μL, 3.57 mmol, 10 mol %). Reaction time: 3 h. Yield 8.0 g (70.0%).

MS 319 ($M+H^+$)

^1H NMR (CD_3OD) δ 7.78 (s, 1H), 7.65 (d, 1H), 7.45 (d, 1H), 6.18 (s, 1H), 3.56 (m, 2H), 3.26 (m, 1H), 2.40 (s, 3H), 1.13 (s, 9H).

H-Tyr(*t*-Bu)-AMC (Formula II)

[00033] Fmoc-Tyr(*t*-Bu)-AMC (Formula I) (41.4 g, 67.1 mmol), 1-octanethiol (116.5 mL, 671 mmol), DBU (3 mL, 20.0 mmol, 30 mol %). Reaction time: 24 h. Yield 15.8 g (59.8%).

MS 395 ($M+H^+$)

^{1}H NMR (CD_3OD) δ 7.65-7.34 (m, 3H), 7.10 (d, 2H), 6.84 (d, 2H), 6.18 (s, 1H), 3.69 (t, 1H), 2.94 (m, 2H), 2.39 (s, 3H), 1.92 (s, 9H).

H-Asp(O-*t*-Bu)-AMC (Formula II)

[00034] Fmoc-Asp(O-*t*-Bu)-AMC (Formula I) (34.5 g, 60.8 mmol), 1-octanethiol (105.4 mL, 608 mmol), DBU (1.8 mL, 12.0 mmol, 20 mol %). Reaction time: 28 h. Yield 16.8 g (79.7%).

MS 347 ($M+H^+$)

^{1}H NMR (1:1 $CDCl_3/CD_3OD$) δ 7.52 (s, 1H), 7.35 (d, 1H), 7.24 (d, 1H), 5.94 (s, 1H), 3.55 (t, 1H), 2.49 (m, 2H), 2.18 (s, 3H), 1.17 (s, 9H).

H-Glu(O-*t*-Bu)-AMC (Formula II)

[00035] Fmoc-Glu(O-*t*-Bu)-AMC (Formula I) (39.7 g, 68.1 mmol), 1-octanethiol (118.1 mL, 681 mmol), DBU (1.02 mL, 6.81 mmol, 10 mol %). Reaction time: 48 h. Yield 22.1 g (90.2%).

MS 361 ($M+H^+$)

^{1}H NMR (CD_2Cl_2) δ 9.86 (br s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.51 (d, 1H), 6.18 (s, 1H), 3.53 (m, 1H), 2.43 (s, 3H), 2.04 (m, 2H), 1.61 (m, 2H), 1.47 (s, 9H).

H-Thr(*t*-Bu)-AMC (Formula II)

[00036] Fmoc-Thr(*t*-Bu)-AMC (Formula I) (20.8 g, 37.6 mmol), 1-octanethiol (65.2 mL, 376 mmol), DBU (562 μL, 3.76 mmol, 10 mol %). Reaction time: 5 h. Yield 6.0 g (74.2%).

MS 333 ($M+H^+$)

^{1}H NMR (CD_3OD) δ 7.81 (s, 1H), 7.69 (d, 1H), 7.46 (d, 1H), 6.20 (s, 1H), 4.05 (m, 1H), 3.21 (m, 1H), 2.42 (s, 3H), 1.18 (d, 3H), 1.13 (s, 9H).

H-Trp(Boc)-AMC (Formula II)

[00037] Fmoc-Trp(Boc)-AMC (Formula I) (10.7 g, 15.7 mmol), 1-octanethiol (27.3 mL, 157 mmol), DBU (235 μL, 1.57 mmol, 10 mol %). Reaction time: 19 h. Yield 5.6 g (77.8%).

MS 462 ($M+H^+$)

^{1}H NMR (CD_3OD) δ 8.04-7.12 (m, 8H), 6.18 (s, 1H), 3.74 (t, 1H), 3.09 (m, 2H), 2.40 (s, 3H), 1.55 (s, 9H).

H-Arg(Pbf)-AMC (Formula II)

[00038] Fmoc-Arg(Pbf)-AMC (Formula I) (19.6 g, 24.3 mmol), 1-octanethiol (42.2 mL, 243 mmol), DBU (728 μL, 4.87 mmol, 20 mol %). Reaction time: 19 h. Yield 8.63 g (60.8%).

MS 584 ($M+H^+$)

^1H NMR (CD_3OD) δ 7.18 (m, 1H), 7.66 (m, 1H), 7.47 (m, 1H), 6.19 (s, 1H), 3.53 (m, 2H), 3.43 (t, 1H), 3.15 (m, 2H), 2.91 (s, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H), 1.99 (s, 3H), 1.38 (s, 6H), 1.25 (m, 2H).

H-Asn(Trt)-AMC (Formula II)

[00039] Fmoc-Asn(Trt)-AMC (Formula I) (47.2 g, 62.5 mmol), 1-octanethiol (108.5 mL, 625 mmol), DBU (935 μL, 6.25 mmol, 10 mol %). Reaction time: 22.5 h. Yield 27.0 g (81.1%).

MS 532 ($M+H^+$)

^1H NMR (CD_2Cl_2) δ 10.0 (br s, 1H), 7.82-7.19 (m, 18H), 6.18 (s, 1H), 3.72 (br s, 1H), 3.36 (m, 1H), 2.84 (m, 2H), 2.43 (s, 3H).

H-Gln(Trt)-AMC (Formula II)

[00040] Fmoc-Gln(Trt)-AMC (Formula I) (48.7 g, 63.4 mmol), 1-octanethiol (110.0 mL, 634 mmol), DBU (948 μL, 6.34 mmol, 10 mol %). Reaction time: 21.5 h. Yield 28.9 g (83.6%).

MS 546 ($M+H^+$)

^1H NMR (CD_2Cl_2) δ 9.85 (br s, 1H), 7.76 (s, 1H), 7.57 (d, 1H), 7.41 (d, 1H), 7.36-7.22 (m, 15H), 6.17 (s, 1H), 3.41 (m, 1H), 2.52 (t, 2H), 2.42 (s, 3H), 2.03 (m, 2H).

H-Cys(Trt)-AMC (Formula II)

[00041] Fmoc-Cys(Trt)-AMC (Formula I) (56.7 g, 76.4 mmol), 1-octanethiol (132.5 mL, 764 mmol), DBU (1.14 mL, 7.64 mmol, 10 mol %). Reaction time: 30 h. Yield 33.8 g (88.2%).

MS 521 ($M+H^+$)

^1H NMR (CD_2Cl_2) δ 9.64 (br s, 1H), 7.69-7.22 (m, 18H), 6.16 (s, 1H), 3.24 (m, 1H), 2.75 (m, 2H), 2.41 (s, 3H).

[00042] Each of the patent applications, patents, publications, and other published documents mentioned or referred to in this specification is herein incorporated by reference in its entirety, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

[00043] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention and the appended claims. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, method, process step or steps, to the

objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.